REMARKS

Claim Amendments

Claims 1-31, 34, and 35 are pending. Claims 34 and 35 are newly added. Claims 3, 13, 14, and 26-30 stand withdrawn. Claims 32 and 33 are canceled without prejudice or disclaimer to the subject matter therein. Applicants respectfully reserve the right to file continuations and/or divisionals directed to the canceled subject matter. Support for new claims 34 and 35 may be found throughout the specification and original claims as filed. *See, e.g.*, Specification, page 11, lines 1-5; page 16, lines 6-15; page 29, lines 5-11; page 30, lines 6-19; page 34, lines 7-13. No new matter has been added.

Statement of Substance of Interview Under 37 C.F.R. § 1.133(b)

In accordance with 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04, Applicants provide a summary of the interview among Applicants' representatives and Examiners Falk and Sgagias conducted on August 11, 2008 ("the interview"). Applicants thank the Examiners for agreeing to conduct the interview and appreciate the courtesies extended by the Examiners.

During the interview, Applicants' representatives explained that the cited references alone, or in combination, do not teach element (c) of claims 1 and 2. Applicants' representatives also pointed out that Poolman relates to neonatal cardiomyocytes in a transgenic mouse model (i.e., knockout mouse), whereas the claimed invention relates to methods of proliferating neonatal cardiomyocytes and cardiomyocytes that have withdrawn from the cell cycle (e.g., adult cardiomyocytes). The Examiners authorized Applicants to file a Supplemental Amendment and response.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4-12, 15-25, and 31 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tamamori-Adachi, *et al.* (2003) Circ. Res. 92:e12-e19 ("Adachi") taken with Sutterlüty, *et al.* (1999) Nature Cell Biology 1: 207-214 ("Sutterlüty"); Sherr, *et al.* (1999) Genes & Development 13:1501-1512 ("Sherr"); Flink, *et al.* (1998) J. Mol. Cell. Cardiol. 30: 563-578 ("Flink"); and Poolman, *et al.* (1999) Circ. Res. 85: 117-127 ("Poolman").

Applicants respectfully traverse this rejection.

A. The References Do Not Teach Or Suggest The Claimed Invention

The Office Action asserts that Adachi teaches a method for proliferating cardiomyocytes *in vitro* comprising introducing a cyclin (linked to nuclear localization signal) and a cyclin-dependent kinase (CDK), but does not teach "the introduction of a gene encoding a factor that inhibits the

production or function of Cip/Kip family proteins into cardiomyocyte cultures." Office Action, pages 3-4. The Office Action contends, however, that it would have been obvious to introduce such a gene into Adachi's system in view of Sutterlüty, Sherr, Flink, and Poolman.

Applicants respectfully disagree and submit that the references alone, or in combination, do not teach introducing a gene encoding a factor that inhibits the production or function of a Cip/Kip protein (e.g., of $p27^{kip1}$) into a cardiomyocyte *in vitro*. As discussed in Applicants' previous response, neither Sutterlüty nor Sherr directly relates to cardiomyocytes or methods of proliferating cardiomyocytes. *See* Response filed July 28, 2008, page 8. Flink relates to cardiomyocytes, but is primarily concerned with the role of retinoblastoma protein (pRb) in the withdrawal from the cell cycle, and does not teach or suggest introducing a gene encoding a factor that inhibits the production or function of a Cip/Kip protein. Flink, page 574.

Poolman's disclosure is limited to the developmental effects of the absence of p27 in neonatal cardiomyocytes. Poolman, at best, suggests that a genetically engineered mouse *never having* $p27^{kip1}$ (i.e., $p27^{kip1}$ knockout mouse) showed "prolonged proliferation of cardiac myocytes and a perturbation of cardiac myocyte hypertropy and differentiation." Poolman, page 126. As can be appreciated by one of ordinary skill in the art, the developmental events influenced by the absence of $p27^{kip1}$ during development are not identical to inhibiting a Cip/Kip protein.

Applicants further submit that one of ordinary skill in the art would not extrapolate the teachings of Poolman to create an exogenous factor that inhibits a Cip/Kip protein. Even if one created such a factor, the specification demonstrates that almost no increase in the cell number of cardiomyocytes was observed where the production of $p27^{Kip1}$ gene product was inhibited by infection with p27 siRNA alone. *See* Specification, Example 5 and Figures 9 and 10; *see also* page 82, lines 8-11 ("Almost no increase of the cell numbers of cardiomyocytes infected with ... Ad-p27 siRNA alone as negative controls was observed."). In view of the failure of the inhibition of p27 alone to increase cardiomyocyte proliferation, one of ordinary skill in the art would have no reason to combine Poolman with the other references, nor would there be a reasonable expectation of success if the references were combined.

B. The Combination Of References Do Not Teach Or Suggest Methods Of Proliferating Cardiomyocytes That Have Withdrawn From The Cell Cycle

New claims 34 and 35 are drawn to methods of proliferating cardiomyocytes that have withdrawn from the cell cycle (e.g., adult cardiomyocytes). The combination of references do not teach or suggest such methods. Indeed, as discussed in Applicants' previous response and in the interview, Poolman relates only to neonatal transgenic cardiomyocytes (i.e., $p27^{kip1}$ knockout mice), and does not relate to cardiomyocytes that have withdrawn from the cell cycle (e.g., adult cardiomyocytes). *See* Response filed July 28, 2008, pages 8 and 9. Additionally, the disclosure of Poolman is drawn to analysis of the effect of the absence of $p27^{kip1}$ during development on neonatal cardiomyocytes and not the blockage of a Cip/Kip protein in cardiomyocytes that have withdrawn from the cell cycle (e.g., adult cardiomyoctes). Adult cardiomyocytes can be recognized by their morphological, physiological, and immunological features. *See e.g.*, Specification, page 16, lines 6-15. Adult cardiomyocytes are cardiomyocytes with little or no proliferative activity, expressing at least one cardiomyocyte marker (e.g., ion channels). *See, e.g.*, Specification, page 11, lines 1-5; page 16, lines 6-15; page 29, lines 5-11; page 30, lines 6-19; page 34, lines 7-13.

In view of the foregoing, Applicants respectfully request withdrawal of the obviousness rejection over Adachi, Sutterlüty, Sherr, Flink, and Poolman.

CONCLUSION

Applicants respectfully submit that claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this response, the Examiner encouraged to contact the Applicants' undersigned representative to discuss and resolve such issues.

It is believed that no fees are necessary for the submission of this response. However, should the USPTO determine that any fees are due in connection with this response, the USPTO is hereby authorized to charge such fees to the undersigned's **Deposit Account No. 50-0206.**

Respectfully submitted,

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